

ntagonists

rgos PGYRYLFA[—]CSP-LTRLRCQKQPC[—]KLFTTVKRQEF[—]LDENVNINSLCQC[—]PK---GHRCPSSHHTQSG- D. melanogaster

gonists

in-3 IEKLKEAKCKD-----YCHHNATCHEVEIFRED---RVSAVVPSC[—]HPQGWEGTRC[—]DRHYVQAF- C. elegans

ein DRASGIPCN--FD--YCFHNGTCRMI[—]PDIN-----EYI--CRCPTEYF[—]GNRCENKWPDSR- D. melanogaster
 arken ETEIQMLPCSEAYNTSF[—]CLNGGHC[—]FQHPMVNN-----TVFHS[—]CLCVNDYDGER[—]CAYKSWNGD- D. melanogaster
 pitz NITFPTYKCPETFD[—]AWYCLND[—]AHCFAVKIADL-----PVYS-CECAIGFM[—]QORCEYKEIDNT- D. melanogaster
 aren NVTFFI[—]FA[—]CPPTYVAWYCLNDGTCT[—]TVKIHNE-----ILYN-CECALGFM[—]GPRCEYKEIDGS- D. melanogaster

RG1_alpha

TGTSHLVKCAEKEKT-FCVNGGEC[—]FMVKDLS-----NPSRYLCKCQ[—]PGTGARTENVPMKV- Homo sapiens

RG1_beta

TGTSHLVKCAEKEKT-FCVNGGEC[—]FMVKDLS-----NPSRYLCKCPNEFT[—]GDRCQNYVMAS- Homo sapiens

RG2_alpha

SWSGHARKCNETAKS-YCVNGGV[—]CYYIEGIN-----QLS---CKCPNGFF[—]GORCLEKPLRL- Homo sapiens

RG2_beta

SWSGHARKCNETAKS-YCVNGGV[—]CYYIEGIN-----QLS---CKCPVGYT[—]GDRCQQFAMVNF- Homo sapiens

RG3

ERSEHF[—]KPC[—]RD[—]KDLA-YCLNDGEC[—]FVIE[—]TLTG-----SHK--HCRCKEGYQ[—]GVRC[—]DQ-FLPKTD Homo sapiens

RG4

MPTDHEEP[—]CGPSHKS-FCLNGGL[—]CYVIPTIP-----SP---FCRCVENYT[—]GARCEEVFLPGS- Homo sapiens

3F

SVRNSDSE[—]CLSHDG-YCLHDGV[—]CMYIEALD-----KYA---CNCVVG[—]YIGERCQYRD[—]LKWW- Homo sapiens

3F_alpha

AVVSHFND[—]CPDSHTQ-FCFH-GT[—]CRFLVQED-----KPA---CVCHSGYV[—]GARCEHAD[—]LLAV- Homo sapiens

stacellulin

KRKGHFSR[—]CPKQYKH-YCIK-GR[—]CRFVVAEQ-----TPS---CVDEGYI[—]GARCERVD[—]DLFYL- Homo sapiens

aphiregulin

RNRKKNP[—]CNAEFQN-FCIH-GE[—]CKYIEHLE-----AVT---CKCQ[—]QYFGER[—]CGEKSMKTH- Homo sapiens

3-EGF

GLGKKRDP[—]CL[—]RYKD-FCIH-GE[—]CKYV[—]KELR-----APS---CICH[—]PGYHGER[—]CHGLSLPVE- Homo sapiens

piregulin

VAQVSITK[—]CSSDMNG-YCLH-GQ[—]CIYLVDMS-----QNY---CRCEVGYT[—]GVRC[—]EHFFLTVH- Homo sapiens

nigen

VALKFSHP[—]CLEDHNS-YCIN-GA[—]CAFHH[—]ELK-----QAI---CR[—]CTGYT[—]GORCEH[—]LLT[—]TSY- Mus musculus

nserved cysteine #: 1 2 3 4 5 6

FIGURE 1

Replacement Sheet

[illegible]

FIGURE 2

Sequence ID #

NRG1_alpha	1	TGTSHLVKAEKEKTFVNGGECFMVKDLSNPSRYLCKQCPGFTGARCTENVPMKV
NRG1_beta	2	TGTSHLVKAEKEKTFVNGGECFMVKDLSNPSRYLCKCPNEFTGDRCONYVMASF
NRG2_alpha	3	SWSGHARKCNETAKSYCVNGGVYYIEGINQLS---CKCPNGFFGQRCLEKLPRL
NRG2_beta	4	SWSGHARKCNETAKSYCVNGGVYYIEGINQLS---CKCPVGYTGDRCCQGFAMVNF
NRG3	5	ERSEHFKPCRDKDLAYCLNDGECFVLETLTGSHK-HCRCKEGYQGVRCDOFLPKTD
NRG4	6	MPTDHEEPCGSPSHKSFCLNGGLCYVVIPTIP--SP-FCRCVENYTGARCEEVFLPGS
EGF	7	SVRNSDSECPLSHDGYCLHDGVCNMYIEALDKYA---CNCVVGYIGERCQYRDLKWW
TGF_alpha	8	AVVSHFNDCPDSTHTQCFH-GTCRFLVQEDKPA---CVCHSGYVGARCEHADLLAV
Betacellulin	9	KRKGFHSRCPKQYKHYCIK-GRCRFVVAEQTPS---CVCDEGYIGARCERVDLFYL
Amphiregulin	10	RNRKKKNPCNAEFQNFCH-GECKYIEHLEAVT---CKCQOEYFGERCCEKSMKTH
HB-EGF	11	GLGKKRDPCLRKVKDFCIH-GECKYVVKELRAPS---CICHPGVHGERCHGLSLPVE
Epiregulin	12	VAQVSIKCSDDMNGYCLH-GQCIYLVDMSONY---CRCEVGYTGVRCEHFFLTVH
Epigen	13	VALKFSPCLIEDHNSYCIN-GACAFHHLEKQAI---CRCFTGYTGQRCHEHLTLTSY

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FIGURE 3

HUMAN	Exon A	Exon B	Sequence ID #
	<-----	----->	----->
NRG1_alpha	...TGTSHLVKCAEKEKTF	CVNGGECFMVKDLSNPSRYLCKQPGFTGARTENVPMKVQ...	14
NRG1_beta	...TGTSHLVKCAEKEKTF	CVNGGECFMVKDLSNPSRYLCKPNEFTGDRCCQNYVMASFY...	15
Translated genomic locus	...TGTSHLVKCAEKEKTF	CVNGGECFMVKDLSNPSRYLCK*	73, 128
NRG2_alpha	...SWSGHARKCNETAKSY	CVNGGVCCYYIEGINQLS---CKCPNGFFGQRCLEKLPLRLY...	16
NRG2_beta	...SWSGHARKCNETAKSY	CVNGGVCCYYIEGINQLS---CKCPVGYTGDRCCQFAMVNFY...	17
Translated genomic locus	...SWSGHARKCNETAKSY	CVNGGVCCYYIEGINQLS---CK*	74, 129
NRG3	...ERSEHFKPCRDKDLAY	CLNDGECFVIETLTGSH-KHCRCKEGYQGVRCDDQ-FLPKTD...	18
Translated genomic locus	...ERSEHFKPCRDKDLAY	CLNDGECFVIETLTGSH-KHCR*	75, 130
NRG4	MPTDHEEP	CGPSHKSFCLNGGLCYVIPTIPSPF---	19
Translated genomic locus	MPTDHEEP	CGPSHKSFCLNGGLCYVIPTIPSPF---CR*	76, 131
EGF	...SVRNSDSECP	LSHDGYCLHDGVCMYIEALDKYA---	20
Translated genomic locus	...SVRNSDSECP	LSHDGYCLHDGVCMYIEALDKYA---CK*	77, 132
TGF_alpha	...AVVSHFND	CPDSHTQFCFH-GTCRFLVQEDKPA---	21
Translated genomic locus	...AVVSHFND	CPDSHTQFCFH-GTCRFLVQEDKPA---CV*	78, 133
Betacellulin	...KRKGHFSRCPKQKHYCIK	-GRCRFVVAEQTPS---	22
Translated genomic locus	...KRKGHFSRCPKQKHYCIK	-GRCRFVVAEQTPS---CV*	79, 134

FIGURE 4A

Amphiregulin	...	PNRKKKNP	CNAEFQNF	CIH-GECKYIEHLEAVT	---CKCQQ	EYFG	ERC	GKSMK	THS....	23
Translated genomic locus	...	PNRKKKNP	CNAEFQNF	CIH-GECKYIEHLEAVT	---CK*					80, 135
HB-EGF	...	GLGKKRDP	CLRKYKDF	CIH-GECKYVVKELRAPS	---CICH	PGYHGER	CHGL	SLPVEN	...	24
Translated genomic locus	...	GLGKKRDP	CLRKYKDF	CIH-GECKYVVKELRAPS	---CM*					81, 136
Epiregulin	...	VAQVSITK	CSSDMNGY	CLH-GQCIYLV	DMSQNY	---CRCE	VGYTG	VRC	EHFFLTVHQ...	25
Translated genomic locus	...	VAQVSITK	CSSDMNGY	CLH-GQCIYLV	DMSQNY	---CR*				82, 137
Epigen (Mouse)	...	VALKFSHP	CLEDHNSY	CIN-GACAFH	HELKQAI	---CRC	FTGYTG	QRC	EHLLTTSYA...	26
Trans. mouse genomic locus	...	VALKFSHP	CLEDHNSY	CIN-GACAFH	HELKQAI	---CR*				83, 138
Trans. mouse genomic locus	...	IALKFSHL	CLEDHNSY	CIN-GACAFH	HELEKAI	---CR*				84, 139

FIGURE 4B

Replacement Sheet

i) TGF alpha Sequence ID #
 EGF DOMAIN NUMBER -----SEQUENCE-----
 1. EGF_47_82* CPDSHTQFCF-HGT-CRFLVQEDKPACVCHSG--YVGAR--C 72

ii) EPIDERMAL GROWTH FACTOR Sequence ID #
 EGF DOMAIN NUMBER -----SEQUENCE-----
 1. EGF_318_354 CKLR-KGNCS--STVCGQDL--QSHLCMCAEGYALSRDRKYC 27
 2. EGF_360_395 CAFW-NHGC---TLGCKNTP--GSYYCTCPVGFVLLPDGKRC 28
 3. EGF_401_436 CPRN-VSEC---SHDCVLTS--EGPLCFCPEGSVLERDGKTC 29
 4. EGF_439_476 CSSPDNGGCS--QLCVPLSP--VSWECDCFPGYDLQLDEKSC 30
 5. EGF_745_780 CLYQ-NGGC---EHICKRRL--GTAWCSCREGFMKASDGKTC 31
 6. EGF_835_868 CAPV---GCS-MYARCISEG--EDATCQCLKG--FAGDGKLC 32
 7. EGF_874_910 CEMG-VPVCPPASSKCINTE--GGYVCRCSEG--YQGDGIHC 33
 8. EGF_916_951 CQLG-VHSCGENAS-CTNTE--GGYTMCAGR--LSEPGLIC 34
 9. EGF_976_1012* CPLSHDGYCL-HDGVCMYIEALDKYACNCVVG--YIGER--C 35

FIGURE 5B

iii) Notchl

Sequence ID #

EGF DOMAIN NUMBER	SEQUENCE	
1. EGF_24_57	CSQ-----PGETCLNGGKCEAANGTE-----ACVCG-GAFVVGPRC	36
2. EGF_63_98	CLS-----TPCKNAGTCH-VVDRRGVADYACSCA-LGFSGPLC	37
3. EGF_106_138	CLT-----NPCRNGGTCD-LLTLT---EYKCRCP-PGWSGKSC	38
4. EGF_144_175	CAS-----NPCANGGQC---LP-FEASYICHCP-PSFHGPTC	39
5. EGF_182_215	CGQ-----KPRLCRHGGTCHNEVGSY-----RCVCR-ATHTGPNC	40
6. EGF_222_254	CSPSP-----CQNGGTCRPTGDV-----THECACL-PGFTGQNC	41
7. EGF_261_292	CPGNN-----CKNGGACV-DGVN----TYNPCPCP-PEWTGQYC	42
8. EGF_299_332	CQL-----MPNACQNGGTCHNTHGGY-----NCVCV-NGWTGEDC	43
9. EGF_339_370	CAS-----AACFHGATCH-DRVA----SFYCECP-HGRTGLLC	44
10. EGF_376_409	CIS-----NPCNEGSNCD-TNPV---NGKAICTCP-SGYTGPA	45
11. EGF_416_449	CSL-----GANPCEHAGKCINTLGSF-----ECQCL-QGYTGPRC	46
12. EGF_456_487	CVS-----NPCQNDATCL-DQIG---EFQCMCM-PGYEGVHC	47
13. EGF_494_525	CAS-----SPCLHNGRCL-DKIN---EFQCECP-TGFTGHLC	48
14. EGF_532_563	CAS-----TPCKNGAKCL-DGPN---TYTCVCT-EGYTGTHC	49
15. EGF_570_600	CDPDP-----CHYG-SCK-DGVA---TFTCLCR-PGYTGHH	50
16. EGF_607_638	CSS-----QPCRLRGTCQ-DPDN---AYLCFCL-KGTTGPNC	51
17. EGF_645_675	CAS-----SPC-DSGTCL-DKID---GYECACE-PGYTGSMC	52
18. EGF_682_713	CAG-----NPCHNGGTC---ED-GINGFTCRCP-EGYHDPTC	53
19. EGF_720_750	CNS-----NPCVHGACRD---SLN---GYKCDGD-PGWSGTNC	54
20. EGF_757_788	CES-----NPCVNGGTCK-D-MTS---GIVCTCR-EGFSGPNC	55
21. EGF_795_826	CAS-----NPCLNKGTC---IDD---VAGYKCNCL-LPYTGATC	56
22. EGF_833_867	CAP-----SPCRNGGECR-QSED-YES-FSCVCPTAGAKQTC	57
23. EGF_874_905	CVL-----SPCRHGASCQ-NTHG---XYRCHCQ-AGYSGRNC	58
24. EGF_912_943	CRPNP-----CHNGGSCT-DGIN---TAFCDCL-PGFRGTFC	59
25. EGF_950_981	CAS--DP-----CRNGANCT-DCVD---SYTCTCP-AGFSGIHC	60
26. EGF_988_1019	CTESS-----CFNGGTCV-DGIN---SFTCLCP-PGFTGSYC	61
27. EGF_1026_1057	CDS-----RPCLLGGTCQ-DG---RGLHRCTCP-QGYTGPN	62
28. EGF_1064_1095	CDS-----SPCKNGGKCW-QT---HTQYRCECP-SGWTGLYC	63
29. EGF_1102_1143	CEVAAQRQGVVDVARLCQHGGLCV-DAGN---THHCRCQ-AGYTG	64
30. EGF_1150_1181	CSP-----SPCQNGATCT-DYLG---GYSCKCV-AGYHGVNC	65
31. EGF_1188_1219	CLS-----HPCQNGGTCL-DLPN---TYKCSCP-RGTQGVHC	66
32. EGF_1226_1265	CNPPVDPVSR--PKCFNNGTCV-DQVG---GYSCTCP-PGFVG	67
33. EGF_1272_1305	CLS-----NPCDARGTON-CVQR---VNDFHCECR-AGHTG	68
34. EGF_1312_1346	CKG-----KPCCKNGGTCA-VASN-TARGFICKCP-AGFEGATC	69
35. EGF_1353_1384	C-----GSLRCLNGGTCTISGPRSP-----TCLCL-GPFTG	70
36. EGF_1392_1426	CL-----GGNPCYNQGTCEPTSESPF---YRCLCP-AKFNGLLC	71

FIGURE 5C

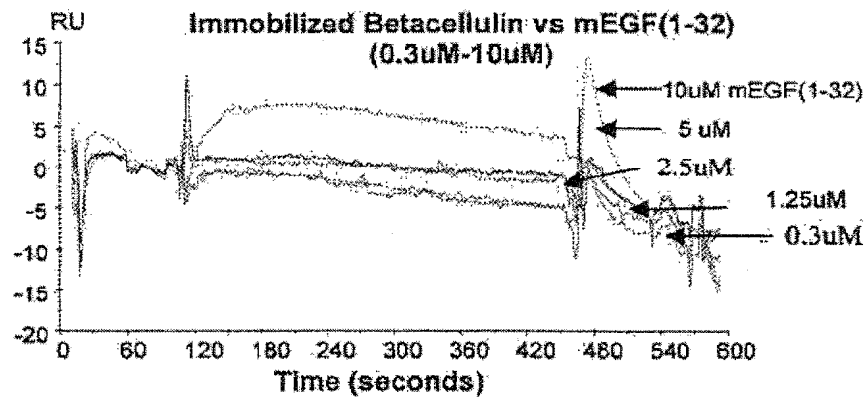


FIGURE 6A

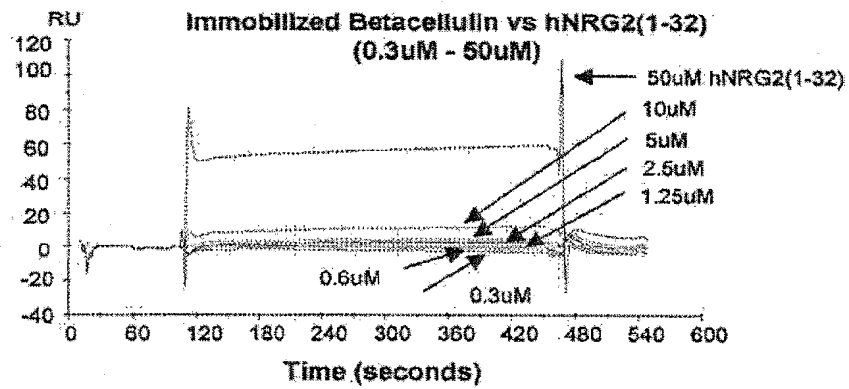


FIGURE 6B